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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/627,796	07/28/2000	Krishan L. Taneja	BP9806US-CP2	3581

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EXAMINER
SOUAYA, JEHANNE E

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/627,796	TANEJA, KRISHAN L.	
	Examiner	Art Unit	
	Jehanne E Souaya	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *26 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *16-20 and 24-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15,21-23 and 29-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5/2001* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group II, chromosome Y, sequences 10-16 in the reply dated 3/5/2002 is acknowledged. The traversal is on the ground(s) that a restriction requirement cannot be imposed to a single claim. The response cites *In re Weber*. Further, the response asserts that each of the groups is classified under the same class and subclass and that no additional burden is placed on the office. Additionally, the response asserts that the claims are generic and use proper Markush format. These arguments have been thoroughly reviewed but were not found persuasive. The function of each probe, that is, the ability to hybridize to a specific chromosome, is dependent on its structure, that is, it's nucleobase composition. Although this nucleobase containing portion is not a nucleic acid, it functions in hybridization through Watson Crick or Hoogstein base pairing and recognizes a DNA sequence through its ability to hybridize using Watson Crick or Hoogstein base pairs. A probe, whether nucleic acid or PNA, which comprises a nucleobase containing portion as outlined in SEQ ID NO 1 and specifically detects chromosome X is patentably distinct from a probe, whether nucleic acid or PNA, which comprises a nucleobase containing portion as outlined in SEQ ID NO 10, and specifically detects chromosome Y. These probes have different functions, and presumably, as the specification teaches that they are specific for specific chromosomes, the probe with a nucleobase containing portion of SEQ ID NO 1 will not detect chromosome Y. Probes that detect chromosome X are not functionally equivalent to probes that detect chromosome Y. The response asserts that the claims are generic in nature. This argument was not found persuasive

because, as set forth in the specification, the probing nucleobase sequence is the sequence recognition portion of the construct (see p. 19, lines 26-27) and is responsible for the function of the molecule. Further, the specification teaches that each nucleobase portion was derived from specific regions for each specific chromosome (see pp 53-54, "Design of Chromosome Specific Probes"). While a PNA probe with a nucleobase containing portion of SEQ ID NO 1 and a PNA probe with a nucleobase containing portion of SEQ ID NO 10 are both PNAs, a polymerase and a ligase are also both proteins, however they are patentably distinct because the specific composition of amino acids for each molecule make them structurally and functionally different. The assertion that searching all the groups provides no additional search burden on the office is unpersuasive as the search is not limited to searching in classes and subclasses of the patent literature. The claims are drawn to 18 different chromosome or chromosome pairs, and 159 different nucleobase containing sequence, thus making the burden to search these chromosomes which comprises billions of sequences, as well as the probes, extremely high on both the examiner and the office. Therefore, the requirement is still deemed proper and is therefore made FINAL.

2. It is noted that the response indicates group II and sequences 10-16, however it also identifies such as chromosome X. The previous restriction requirement set forth methods and sequences to chromosome Y in group II. As this group corresponds to SEQ ID NOS 10-16, the examiner assumes that the indication of chromosome X was in error. Accordingly, an action on the merits of group II, claims 1-15, 21-23, and 29-45, corresponding to chromosome Y and SEQ ID NOS 10-16 follows.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-15, 21-23 and 29-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a PNA probe with N-[2-(aminoethyl)] glycine backbones consisting of nucleobases from the group consisting of SEQ ID NOS 10-16, does not reasonably provide enablement for a probe set comprising any non nucleic acid probes for chromosomes Y, or a probe or probe set comprising any non nucleic acid probes "having" a nucleobase containing portion of SEQ ID NOS 10-16, or to a probe set comprising non nucleic acid probes "having" a probing nucleobase sequence at least a portion of which is at least ninety percent homologous to the nucleobase sequence or their complements of SEQ ID NOS 10-16, or to methods using or kits comprising such probes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are broadly drawn to any *non nucleic acid* probes for chromosomes Y or a probe or probe set comprising any non nucleic acid probes "having" a nucleobase containing portion of SEQ ID NOS 10-16, or to a probe set comprising non nucleic acid probes "having" a probing nucleobase sequence at least a portion of which is at least ninety percent homologous to the nucleobase sequence or their complements of SEQ ID NOS 10-16, or to methods using or kits comprising such probes. The specification defines "non nucleic acid probes" as a probe comprising a probing nucleobase sequence which is designed to hybridize to at least a portion of

a target sequence, such as a PNA probe. The specification further defines "PNA" as any oligomer, linked polymer, or chimeric oligomer, including PNA-DNA chimeras, comprising two or more PNA subunits, nucleic acid mimics, and peptide based nucleic acid mimics. The specification teaches that a use for the probes of the claimed invention are for improving the specificity, sensitivity and reliability of probe based assays for the detection of chromosomes Y. The specification teaches the specific constructs of table 2 with the specific nucleobase containing portions outlined in the specification, that is "consisting" of SEQ ID NOS 1-159. The specification demonstrates the use of such as probes as chromosome specific probes. However, the claims are of a much broader scope, such that the specification does not enable the skilled artisan to predictably make or use the claimed products in methods of detecting, identifying, or enumerating specific chromosomes.

The specification teaches that the nucleobase sequence of the non nucleic acid probes is the sequence recognition portion of the construct. However, as outlined above, the term "non nucleic acid probes" encompasses a large number of different types of molecules which the specification has not demonstrated any predictable use for in detecting, identifying or enumerating specific chromosomes. Probes encompassed by all of the claims include for example, PNA probes of undefined length, and PNA-DNA chimeras. It is known, however, that in PNA-DNA chimeras both the PNA nucleobase portion and the DNA portion are involved in hybridization. Therefore, while the specific probes of table 2 have been shown to be specific for identifying a chromosome, it is unpredictable as to whether longer sequences which can comprise an unlimited number of any bases, either PNA or DNA, as illustrated by the broad definitions in the specification, would also exhibit the same properties. While the skilled artisan

would be able to envision some constructs that would seemingly be specific for a particular chromosome using sequence comparison with the sequences in Genbank, the specification teaches that in functional assays, "many of the sequences originally chosen did not prove to be highly specific despite alignment analysis indications that they should be specific to the chromosome sought to be detected" (see p. 24, lines 6-8). Therefore, the specification teaches of the unpredictability in designing chromosome specific probes. Given such teachings, the skilled artisan would not be able to predictably determine the identity of the probing nucleobase containing portions of the probes encompassed by the claims which would be able to function in identifying, detecting, or enumerating human chromosomes Yin a sample, other than by specific SEQ ID NO. Further, while it is known that PNA oligomers hybridize stably with DNA, the art teaches that PNA-DNA chimeras do not share these properties, although theoretical models indicated that they should. For example, Petersen et al (Bioorganic & Medicinal Chemistry Letters, vol 5, pp 1119-1124; 1995) teach that PNA-DNA chimeras hybridize less efficiently to complementary DNA than the parent DNA oligomers indicating that the PNA-DNA 3' junction is not structurally optimal despite a favorable configuration by model building (see p 1123, 2nd para). The post filing date art also illustrates such unpredictability. For example, Capasso et al (Tetrahedron, vol. 57, pp 9481-9486; 2001) teaches that the affinity of PNA DNA chimeras towards target DNA was quite affected by the PNA structure, exhibiting changes in melting temperature of + or – 2 degrees C compared with all DNA sequences, and that such did not appear to be easily explainable (see p. 9483, col. 2, 2nd full para). Capasso also teaches that further experimentation was being undertaken to gain a deeper insight into the behavior of such chimeras. Therefore, the art illustrates the unpredictability that would be involved for the skilled

artisan to make and use the large number of different types of probes encompassed by the broad scope of the claimed invention.

Claims 10, 21, 34, 35 and 45 encompass products, kits containing products, and methods of using products with no specifically defined structure, and such products, while being able to detect a certain chromosome would not necessarily be specific for detecting chromosome X, for example. Probes having a probing nucleobase sequence of undefined length wherein only a portion are 90% homologous to the nucleobase sequence of SEQ ID NO 10, for example (claims 1, 3-9,11, 13-15, 22, 23, 29-33, 36-44) encompass probes, kits comprising probes, and methods of using a probe with only 1 nucleobase in common with SEQ ID NO 10, wherein it is unpredictable as to whether such a probe would be able to be used to detect chromosome Y. Claims 2 and 12, although drawn to exact probing nucleobase sequences (that is, the claim does not encompass sequences, either PNA or DNA or nucleic acid mimics, etc, on either side of the sequence identifier), encompasses probes (due to the broad definitions of "non nucleic acid probes" and "PNA" as outlined in the specification) wherein the specific nucleobase containing portion is a DNA-PNA chimera, for example. However, due to the lack of guidance from the specification and the unpredictability taught in the art, further, undue experimentation would be required of the skilled artisan to make and use the extremely large number of different molecules encompassed by the broad scope of the claimed invention. A large amount of unpredictable trial and error analysis would be required for the skilled artisan to make and use probes as encompassed by the claims. Such experimentation is considered undue.

5. Claims 1-15, 21-23 and 29-45 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to any *non nucleic acid* probes for chromosomes Y or a probe or probe set comprising any non nucleic acid probes "having" a nucleobase containing portion of SEQ ID NOS 10-16, or to a probe set comprising non nucleic acid probes "having" a probing nucleobase sequence at least a portion of which is at least ninety percent homologous to the nucleobase sequence or their complements of SEQ ID NOS 10-16, or to methods using or kits comprising such probes.

The specification defines "non nucleic acid probes" as a probe comprising a probing nucleobase sequence which is designed to hybridize to at least a portion of a target sequence, such as a PNA probe. The specification further defines "PNA" as any oligomer, linked polymer, or chimeric oligomer, including PNA-DNA chimeras, comprising two or more PNA subunits, nucleic acid mimics, and peptide based nucleic acid mimics. The specification teaches that a use for the probes of the claimed invention are for improving the specificity, sensitivity and reliability of probe based assays for the detection of chromosome Y. The specification teaches the specific constructs of table 2 with the specific nucleobase containing portions outlined in the specification, that is "consisting" of SEQ ID NOS 1-159. The specification demonstrates the use of such probes as chromosome specific probes. However, the claims, which recite "non nucleic acid probe", encompass a broad genus of probes including not only PNAs, but PNA-DNA chimeras, nucleic acid mimics, and peptide based nucleic acid mimics. The specification does

not teach of any PNA-DNA chimeras, general nucleic acid mimics or peptide based nucleic acid mimics which comprise a probing nucleobase portion which detects a specific chromosome.

The specification teaches that the nucleobase sequence of the non nucleic acid probes is the sequence recognition portion of the construct. However, as outlined above, the term "non nucleic acid probes" encompasses a large number of different types of molecules which the specification has not demonstrated as specific for any particular chromosome. Probes encompassed by all of the claims include for example PNA-DNA chimeras. It is known, however, that in PNA-DNA chimeras both the PNA nucleobase portion and the DNA portion are involved in hybridization. Therefore, while the specific probes of table 2 have been shown to function as specific for identifying a particular chromosome, the specification does not teach of a predictable structure/function correlation between longer sequences which can comprise an unlimited number of any bases, either PNA or DNA, as illustrated by the broad definitions in the specification. While it is known that PNA oligomers hybridize stably with DNA, the art teaches that PNA-DNA chimeras do not share these properties, although theoretical models indicated that they should. For example, Petersen et al (Bioorganic & Medicinal Chemistry Letters, vol 5, pp 1119-1124; 1995) teach that PNA-DNA chimeras hybridize less efficiently to complementary DNA than the parent DNA oligomers indicating that the PNA-DNA 3' junction is not structurally optimal despite a favorable configuration by model building (see p 1123, 2nd para). Additionally, Capasso et al (Tetrahedron, vol. 57, pp 9481-9486; 2001) teaches that the affinity of PNA DNA chimeras towards target DNA was quite affected by the PNA structure, exhibiting changes in melting temperature of + or – 2 degrees C compared with all DNA sequences, and that such did not appear to be easily explainable (see p. 9483, col. 2, 2nd full para). From such

teachings, the skilled artisan would not be able to determine a predictable structure/ function correlation between PNAs and PNA-DNA chimeras, for example, for the purposes of designing chromosome specific probes. Accordingly, the single type of PNA probe (comprising the "E" subunit as defined on page 47) taught in table 2 are not representative of the large genus of different probes which are encompassed by the claims.

Further, claims 10, 21, 34, 35 and 45, for example, are drawn to probes, methods of using and kits comprising probes with no specifically defined probing nucleobase sequences, and claims 1, 3-9, 11, 13-15, 22, 23, 29-33, 36-44 are drawn to probes with very little specifically defined probing nucleobase sequences (these probes could have as few as 2 or 3 sequential nucleobases in common with any of SEQ ID NOS 10-16). Probes encompassed by these claims include probing nucleobase sequences of undefined length from any part of the genome, including millions of sequences some of which were undefined at the time the specification was filed. However, the probes with sequences outlined in table 2 are not representative of the millions of sequences encompassed by the claims.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 1, 4-11, 13-15, 36-43 and 45 are rejected under 35 U.S.C. 102(e) as being anticipated by Hyldig-Nielsen et al (US Patent 5,985,563; 102(e) date: 5/18/1995).

Hyldig Nielsen teaches a set of PNA probes with a nucleobase containing portion as follows: In table 2, probe 6a comprises the sequence TGC, wherein probe 6a has a sequence a portion of which is 100% homologous to SEQ ID NO 10, probe 6b comprises the sequence CAA, wherein probe 6b has a sequence a portion of which is 100% homologous to SEQ ID NO 11, probe 8b comprises the sequence GGT, wherein probe 8b has a sequence a portion of which is 100% homologous to SEQ ID NO 12, probe 7a comprises the sequence CTT, wherein probe 7a has a sequence a portion of which is 100% homologous to SEQ ID NO 15, probe 9a comprises the sequence AAT, wherein probe 9a has a sequence a portion of which is 100% homologous to SEEQ ID NO 14, probe 8a comprises the sequence AAC, wherein probe 8a has a sequence a portion of which is 100% homologous to SEQ ID NO 16, and probe 9b comprises the sequence TAT, wherein probe 9b has a nucleobase sequence a portion of which is 100% homologous to SEQ ID NO 13. Hyldig-Nielson , probe 26a comprises the sequence AG, probe 27a comprises the sequence GG, probe 28a comprises the sequence GA, probe 29a comprises the

sequence GC, probe 30a comprises the sequence CG, probe 31a comprises the sequence CC, probe 32a comprises the sequence TT, and probe 33a comprises the sequence AT, wherein these probes are have sequences which are100% homologous with probes 1-118 of claim 11. It is noted that the recitation of "which is suitable for detecting, identifying or enumerating chromosomes Y" is considered an intended use, and has been given no patentable weight. Hyldig Nielsen teaches PNA probes can be labeled to unlabeled (col. 9, lines 45-54 and col. 10). Hyldig Nielsen teaches that the probes can be support bound (col. 18). Hyldig Nielsen specifically teaches in situ hybridization with such probes (example 5).

Conclusion

8. No claims are allowable.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703) 308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya

Jehanne Souaya
Patent examiner
Art Unit 1634

4/18/03